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(54) Title: USE OF L-ACETYLCARNITINE, L-ISOVALERYLCARNITINE, L-PROPIONYLCARNITINE FOR INCREASING THE LEVELS OF IGF-1

(57) Abstract

Use of L-acetylcarnitine, L-isovalerylcarnitine, L-propionylcarnitine or pharmacologically acceptable salts thereof for increasing the levels of IGF-1 for the therapeutic treatment or prophylaxis of cytological disorders or diseases related to IGF-1.

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USE OF L-ACETYLCARNITINE, L-ISOVALERYLCARNITINE, L-PROPIONYLCARNITINE FOR INCREASING THE LEVELS OF IGF-I

The present invention relates to a novel therapeutic use of L-acetylcarnitine, L-isovalerylcarnitine, L-propionylcarnitine or pharmacologically acceptable salts thereof for increasing the levels of IGF-1 (insulin-like growth factor 1) for the therapeutic treatment or prophylaxis of cytological disorders or diseases related to IGF-1. More particularly, the present invention relates to the use of L-acetylcarnitine, L-isovalerylcarnitine, L-propionylcarnitine or pharmacologically acceptable salts thereof for the therapeutic treatment or prophylaxis of individuals in whom IGF-1 contributes towards the pathogenesis of a particular disease or provokes cytological disorders.

Like other growth factors, IGF-1 promotes cell growth and differentiation. The administration of IGF-1 obtained as a protein purified by molecular biology methods has made it possible to confirm the effects observed *in vitro* with cells, on animal models and in man. Essentially, the action of IGF-1 is similar to that of insulin, that is to say an increase in the uptake of glucose, a reduction in ketones and fatty acids in the serum and an increase in protein synthesis. In accordance with these and other metabolic effects, clinical studies have been undertaken in order to evaluate the efficacy of IGF-1 in a range of diseases. IGF-1 has been administered to patients with type-II diabetes, to cachectic patients, to patients with ischemic damage at the neuronal, myocardial or renal level, and has been proposed for repairing and regenerating tissues (W.L. Lowe, Insulin-like growth factors, Scientific American Science and Medicine p. 62, March 1996).

From the above, it is clear that the administration of IGF-1 may be therapeutically useful in various morbid conditions. Examples of diseases or disorders which may be prevented, cured or improved by the administration of IGF-1 include neuropathies of the optic nerve

and of the olfactory nerve, neuralgia of the trigeminal nerve, Bell's paralysis, amyotrophic lateral sclerosis and other motor neuron diseases, degeneration of the retina, osteoporosis, arthropathy, arthritis, cervical spondylosis and hernia of the intervertebral discs, clinical syndromes of reduced height, cachexia, acute or chronic hepatic necrosis, Turner's syndrome, sarcopoenia, growth hormone insensitivity syndromes, diabetes, obesity, asthenia in general and in particular myasthenia and heart asthenia, immunodeficiences and reperfusion injuries. IGF-1 moreover appears to be useful for the cicatrization of wounds, the healing of ulcers, the treatment of burns, tissue regeneration in general and in particular that of cutaneous, intestinal and hepatic tissue, and the formation of dentine.

Unfortunately, the administration of IGF-1 in man brings about undesirable effects such as oedema, pain in the temporomandibular joint and arthralgia. These symptoms are such as to prevent the administration of IGF-1 from being recommended or are responsible for interrupting the treatment. It is therefore necessary to find novel substances which are capable of inducing the production of IGF-1.

According to the present invention, the administration of L-acetylcarnitine, L-isovalerylcarnitine, L-propionylcarnitine or pharmacologically acceptable salts thereof is capable of inducing the production of IGF-1 without the undesirable effects produced by the administration of exogenous IGF-1.

In the description which follows, the expression pharmacologically acceptable salt of L-acetylcarnitine, of L-isovalerylcarnitine or of L-propionylcarnitine is understood to refer to any salt of the above with an acid which does not give rise to undesirable toxicity or side-effects. Such acids are well known to pharmacologists and to experts in the pharmaceutical field.

Non-limiting examples of such salts are: chloride; bromide; iodide; aspartate, in particular hydrogen aspartate; citrate, in particular

hydrogen citrate; tartrate; phosphate, in particular hydrogen phosphate; fumarate, in particular hydrogen fumarate; glycero-phosphate, glucose phosphate; lactate; maleate, in particular hydrogen maleate; orotate; oxalate, in particular hydrogen oxalate; sulphate, in particular hydrogen sulphate; trichloroacetate, trifluoroacetate and methanesulphonate.

In the description which follows, for the purposes of brevity and for ease of explanation, reference will be made only to L-acetylcarnitine, it being understood that the description given applies also to the above-mentioned L-isovalerylcarnitine and L-propionylcarnitine and to pharmacologically acceptable salts thereof.

Therapeutic uses of L-acetylcarnitine, L-isovalerylcarnitine and L-propionylcarnitine for the therapeutic treatment of myocardial arrhythmia and ischemia, peripheral functional vasculopathy of the arteries, senile dementia and peripheral neuropathies are already previously known. However, there is no correlation between these known therapeutic uses and the subject of the present invention.

It has now been found, surprisingly, that L-acetylcarnitine, L-isovalerylcarnitine, L-propionylcarnitine or pharmaceutically acceptable salts thereof are capable of increasing the levels of IGF-1 in human biological fluids. It should be emphasized that, on the basis of extensive supporting scientific literature, the mechanism of action of L-acetylcarnitine has been focused at the metabolic level, more specifically demonstrating a protective action with respect to the mitochondria, whereas the present invention demonstrates an action mediated by the production of IGF-1.

In one embodiment of the present invention, the L-acetylcarnitine, L-isovalerylcarnitine, L-propionylcarnitine or pharmaceutically acceptable salts thereof are administered in combination with vasodilatory, vascular, endocrinological, immunological, cytostatic, immunomodulatory, anti-inflammatory or cortisone pharmaceutical

products, IGF-1, IGF-1 binding proteins, growth hormones and other cell growth factors such as, for example, epidermal growth factor, and erythropoietin.

The examples which follow are for the purpose of illustrating the invention and should in no way be understood as implying a limitation in the scope thereof.

Example 1

13 individuals infected with HIV were enroled. Blood was taken before and after treatment with L-acetylcarnitine orally at a dosage of 3 g/day for 8 weeks. The levels of IGF-1 were measured using a kit supplied by Amersham Italia s.r.l., Milan, and the results were expressed as ng of IGF-1/100 µl of serum.

Table 1

Patient #	Before	After
1	0.03	4.16
2	0.03	5
3	0.03	0.06
4	0.02	5
5	0.02	0.05
6	0.04	3.25
7	0.25	5
8	0.02	0.03
9	0.1	5
10	0.07	5
11	0.03	5
12	0.16	3.49
13	0.03	0.18
AVERAGE	0.06	3.17
Standard deviation	0.07	2.22
Standard error	0.02	0.62
Student test		0.0002

It is known that individuals infected with HIV can have variable levels of IGF-1 in their serum. The experiments reported here demonstrated that the oral administration of L-acetylcarnitine increases the levels of IGF-1 in peripheral blood.

Example 2

Four patients aged above 70 and with healthy dispositions were treated with 2 grams/day of L-acetylcarnitine parenterally for 7 days. The results of the doses of IGF-1 before and after the treatment are reported in Table 2.

Table 2

Patient #	Before	After
1	0.01	2.1
2	0.02	3.6
3	0.05	1.8
4	0.03	3.8
AVERAGE	0.03	2.83
Standard deviation	0.02	1.02
Standard error	0.008	0.51
Student test		0.01

Claims

1. Use of L-acetylcarnitine, L-isovalerylcarnitine, L-propionyl-carnitine or pharmacologically acceptable salts thereof for producing a pharmaceutical product for increasing the levels of IGF-1 for the therapeutic treatment or prophylaxis of cytological disorders or diseases related to IGF-1.

2. Use according to Claim 1, for producing a pharmaceutical product for the therapeutic treatment or prophylaxis of neuropathies of the optic nerve and of the olfactory nerve, neuralgia of the trigeminal nerve, Bell's paralysis, amyotrophic lateral sclerosis and other motor neuron diseases, degeneration of the retina, osteoporosis, arthropathy, arthritis, cervical spondylosis and hernia of the intervertebral discs, clinical syndromes of reduced height, cachexia and acute or chronic hepatic necrosis, Turner's syndrome, sarcopoenia, growth hormone insensitivity syndromes, diabetes, obesity, asthenia in general and in particular myasthenia and heart asthenia, immunodeficiences and reperfusion injuries, and for the cicatrization of wounds, the healing of ulcers, the treatment of burns, tissue regeneration in general and in particular that of cutaneous, intestinal and hepatic tissue, and the formation of dentine.

3. Use according to Claim 1 or 2, in which the L-acetylcarnitine, L-isovalerylcarnitine, L-propionylcarnitine or pharmacologically acceptable salts thereof are administered in combination with vasodilatory, vascular, endocrinological, immunological, cytostatic, immunomodulatory, anti-inflammatory or cortisone pharmaceutical products, IGF-1, IGF-1 binding proteins, growth hormones and other cell growth factors [epidermal growth factor, and erythropoietin].

4. Use according to any one of the preceding claims, in which the active principle is L-acetylcarnitine.

5. Use according to any one of Claims 1 to 3, in which the active principle is L-isovalerylcarnitine.

6. Use according to any one of Claims 1 to 3, in which the active principle is L-propionylcarnitine.

7. Pharmaceutical composition which may be administered orally, parenterally, nasally or topically for increasing the levels of IGF-1 for the therapeutic treatment or prophylaxis of cytological disorders or diseases related to IGF-1, this composition comprising, as active principle, an amount of L-acetylcarnitine, L-isovalerylcarnitine, L-propionylcarnitine or of pharmacologically acceptable salts thereof which is effective in increasing the levels of IGF-1, and at least one pharmacologically acceptable excipient.

8. Pharmaceutical composition according to Claim 7, for the therapeutic treatment or prophylaxis of neuropathies of the optic nerve and of the olfactory nerve, neuralgia of the trigeminal nerve, Bell's paralysis, amyotrophic lateral sclerosis and other motor neuron diseases, degeneration of the retina, osteoporosis, arthropathy, arthritis, cervical spondylosis and hernia of the intervertebral discs, clinical syndromes of reduced height, cachexia and acute or chronic hepatic necrosis, Turner's syndrome, sarcopoenia, growth hormone insensitivity syndromes, diabetes, obesity, asthenia in general and in particular myasthenia and heart asthenia, immunodeficiences and reperfusion injuries, and for the cicatrization of wounds, the healing of ulcers, the treatment of burns, tissue regeneration in general and in particular that of cutaneous, intestinal and hepatic tissue, and the formation of dentine, this composition comprising, as active principle, an amount of L-acetylcarnitine, L-isovalerylcarnitine, L-propionyl-carnitine or of pharmacologically acceptable salts thereof which is effective in increasing the levels of IGF-1, and at least one pharmacologically acceptable excipient.

9. Composition according to Claim 7 or 8, which is suitable for the oral, parenteral, nasal or topical administration of 0.01 mg-15 g per day of active principle.

10. Composition according to Claim 7 or 8, which is suitable for the oral, parenteral, nasal or topical administration of 0.1 mg - 10 g per day of active principle.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 516 594 A (SIGMA-TAU INDUSTRIE FARMACEUTICHE RIUNITE SPA) 2 December 1992 see the whole document ---	1,2,5, 7-10
X	WO 95 00137 A (BERNARDINI) 5 January 1995 see the whole document ---	1,2,4, 7-10
X	W.G. SANNITA ET AL.: "Effects of intravenous L-acetylcarnitine on retinal oscillatory potentials." DOC. OPHTHALMOL., vol. 70, 1988, pages 89-96, XP002042648 see the whole document ---	1,2,4,7, 8
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	D.J. PAULSON ET AL.: "Protection of the ischaemic myocardium by L-propionylcarnitine: effects on the recovery of cardiac output after ischaemia and reperfusion, carnitine transport, and fatty acid oxidation." CARDIOVASC. RES., vol. 20, no. 7, 1986, pages 536-541, XP002042649 * abstract *	1,2,4, 6-10
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Information on patent family members

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